mode of action and have activity against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant pneumococci and vancomycin-resistant enterococci. Other novel antibiotics are being developed through chemical modification of existing agents, such as the alteration of the fluoroquinolone nucleus or synthesis of a glycopeptide related to vancomycin. Bacteriophage therapy is being developed to treat multiply resistant *Enterococcus faecium* infections. Furthermore, antisense constructs used alone or as adjuncts to bacteriophage therapy maybe useful for reversing vancomycin resistance. Thus, many approaches are being investigated to combat increasing levels of multiresistant Gram-positive bacteria.

Tul9-5 Meningitis: Consequences of resistance on the choice of treatment

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The empirical management of bacterial meningitis has changed over the past decade as a direct result of decreasing susceptibility to antimicrobials by the major bacterial causes of this disease. Ampicillin and chloramphenicol can no longer be considered for initial therapy; pneumococci are increasingly resistant to penicillins worldwide, and chloramphenicol-resistance remains common in developing countries. Resistance is rapidly spreading through the dissemination of multi-resistant pneumococcal clones. Pneumococci have also acquired resistance to the third-generation cephalosporins, cefotaxime and ceftriaxone. Where cephalosporin resistance is known to occur, the addition of vancomycin should be considered. Strains of *Neisseria meningitidis* resistant to chloramphenicol have emerged, as have strains with intermediate penicillin-resistance. The incidence of chloramphenicol-resistant strains of *Haemophilus influenzae* has increased in frequency in Africa, and betalactamase producing strains remain common worldwide. Gram-negative bacteria and *Listeria* (isolated more rarely in meningitis) also exhibit multiresistance to cephalosporins. Thus there is an urgent need for more active drugs for the treatment of meningitis. The carbapenems have enhanced *in vitro* activity against bacterial pathogens compared with the third-generation cephalosporins. Three randomised comparative trials have compared meropenem with cefotaxime and/or ceftriaxone in bacterial meningitis. Meropenem was as clinically efficacious and as well tolerated as the cephalosporins in these studies. Furthermore, to date there have been no bacteriologically documented failures of meropenem in cephalosporin-resistant pneumococcal meningitis. Current empiric management of meningitis is based on the use of cefotaxime or ceftriaxone plus vancomycin. With increasingly widespread resistance to existing antimicrobial agents, monotherapy with meropenem represents an alternative treatment regimen.

IND14 – Bristol-Myers Squibb

Tul14-1 Control of hospital acquired bacterial resistance: Implications for empiric therapy selection

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Increasing antibiotic resistance of bacterial pathogens is limiting the options for empiric therapy of nosocomial infection. Resistance increases as a result of selection of resistant mutants, acquisition of mobile resistance determinants and epidemic spread of multi-resistant clones. The selection pressure of antibiotic use contributes to all these mechanisms so that interventions aimed at reducing or modulating this selective pressure through antibiotic policy are currently evaluated. In a number of settings, both hospital-wide or in intensive care or oncology department, restriction of prescription of frequently used agents like third generation cephalosporins or fluoroquinolones have been attempted to control resistance to these drugs of nosocomial Gram-negative rods, including *Klebsiella* spp, *Enterobacter* spp and *Acinetobacter* spp. In several studies, this policy, with or without additional infection control measures, appeared effective in reducing the incidence of colonization or infection with multi-resistant strains. In our tertiary care center in a country where multi-resistant *Enterobacter aerogenes* has become endemic, we performed an antibiotic policy intervention in the department of intensive care to reduce the incidence of MR-*E. aerogenes* colonization. Compared to a 6-month baseline, the use of third generation cephalosporins was reduced in the 32-month intervention period by 82%, that of fluoroquinolones by 86% and cefepime was added to the formulary for empiric therapy. We observed a significant and persistent reduction in the resistance of *Enterobacteriaceae* (but not of *Pseudomonas aeruginosa*) to these drugs as well as a significant reduction in the incidence rate of MR-*E. aerogenes*. These data illustrate the usefulness of adapting empiric policy regimens in high-risk hospital units to improve the local ecology of resistance. A rotation strategy may represent a worthwhile option.

Tul14-2 Cefepime for multiple antibiotic resistant GNR infections

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Third-generation cephalosporins (3C) were considered first-line antibiotics for treating serious gram-negative rod (GNR) infections. Recently, expression of AmpC cephalosporinase (AmpC) and extended spectrum β-lactamase (ESBL) in GNR has resulted in widespread resistance to 3C. Cefepime, the new cephalosporin, requires two distinct mutational events for development of resistance, thereby decreasing the likelihood of resistance. Although in vitro data demonstrates the enhanced activity of cefepime against these strains, clinical data is lacking.

Methods: In an 18-month retrospective study, we identified 14 patients treated with cefepime for resistant GNR infections. CDC guidelines were used to identify infection. GNR included in the study had diminished zones of inhibition around 3C, aztreonam, and cefpodoxime disks. Ten of the 14 pathogens were screened for ESBL production by NCCLS guidelines. Clavulate-resistant strains may carry AmpC.

Results: The mean length of stay was 45.4 days, prior antibiotics were used in 12 patients, the mean age of the patients was 52.4 years of age, the male: female ratio was 8:6, and the mean day of GNR acquisition was 26.4. The infection sites included pulmonary (4 p), skin and soft tissue (5 p), and CSF/Bone/Blood/IAA/Urine (5 p).

Pathogens	No. patients	ESBL/ AmpC	Outcomes	Clinical	Bacterial
K pneumoniae	5	3/1	Cure	11	13
K oxytoca	2	1/0	Failure	1	0
E coli	2	2/0	Not evaluable	2	1
E cloacae	5	0/3			

Conclusions: Cefepime was effective in a small number of patients. Larger studies are needed to confirm these results.

Tul14-3 Empiric therapy of nosocomial pneumonia in intensive care unit patients

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Early appropriate antibiotic therapy diminishes mortality in intensive care unit (ICU) patients with nosocomial pneumonia. However, the poor specificity of clinical and microbiological diagnosis of nosocomial pneumonia and the wide array of possible pathogens make the empiric choice of antibiotics difficult. Monotherapy with broad-spectrum antibiotics recently emerged as an appealing option.

Objective: To compare the efficacy of cefepime, 2 g three times a day, and imipenem/cilastatin, 0.5 g four times a day, as monotherapy for ICU patients with nosocomial pneumonia.

Methods: The randomized, open-label, evaluator-blind study was conducted in 13 centers from six European countries. Sixty-six percent of the 270 eligible patients had mechanical ventilation. The mean APACHE II score was 16 at randomization.

Results: Microbiological documentation was available for 180 patients (67%). The most frequent causative organism was Pseudomonas aeruginosa, which occurred in 70 patients. In each group, 86% of the causative organisms were susceptible to the allocated regimen. Success rate (cure or improvement) in intent-to-treat analysis was similar with cefepime (59%) and imipenem/cilastatin (57%). Clinical failure was attributed to resistance of the causative organism in 5.3% of the cefepime patients and 5.8% of the imipenem/cilastatin patients. Among microbiologically documented nosocomial pneumonia, eradication rates were 52% with cefepime and 44% with imipenem/cilastatin. Resistance to the allocated regimen occurred in 4.1% of the causative organisms in cefepime and 6.9% of the causative organisms in imipenem/cilastatin. Nosocomial pneumonia contributed to the death of 11 patients in cefepime and eight patients in imipenem/cilastatin.

Conclusion: We concluded that cefepime and imipenem/cilastatin were active against most of the pathogens causing nosocomial pneumonia in ICU patients and ware clinically equally effective for monotherapy.

Tul14-4 Febrile neutropenia-role and evolution of monotherapy

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Patients with febrile neutropenia have become a significant population in large and specialized medical centers. They comprise a heterogeneous group of patients that have different prognoses and risks for infection. Solid tumor and lymphoma patients make up the largest number of this group followed by leukemia patients, and bone marrow or stem cell transplantation patients. The prognosis of all patients with febrile neutropenia has improved significantly over the past 20 years despite more aggressive therapies for malignancy. Antibiotics have been the most significant improving factor. Antibacterial therapy has improved in treatment approaches and the available drugs. Combination therapy with a β-lactam and an aminoglycoside has been a standard of care since the introduction of carbenicillin in the 1970s. This approach was replaced by more potent antipseudomonal and anti gram-negative drugs. In some areas, ceftazidime or imipenem monotherapy became interchangeable with combination therapy. Certain factors are now driving the evolution of therapy to newer agents, including bacterial resistance and changes in organisms cultured from infections. However, the case for continued monotherapy is stronger because of the introduction of cefepime, fourth-generation cephalosporin, with improved gram-positive and gram-negative activity over ceftazidime and meropenem, a carbapenem. The outpatient use of antibiotics is another direction to manage these patients. Accumulating evidence indicates that patients at lower risk for infection (eg, those with a shorter anticipated duration of neutropenia), may be managed as outpatients and oral antibiotics may be safe. It appears that maximum doses of antibiotics as used in the past may not be needed. The role of fluoroquinolones in this group of patients has clearly been established and newer agents may expand their use. The antibiotic management of febrile neutropenia should include risk determination, knowledge of prevailing resistance patterns and the epidemiology of infections in the institution.

Tul14-5 New alternatives in the empiric treatment of meningitis and other serious pediatric infections

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Hospital-acquired bacterial infections represent a key cause of substantial morbidity and mortality among the pediatric population. It is estimated that almost 10% of hospitalized patients in the United States and Europe will develop an infection during their hospital stay. The most common nosocomial infections afflicting pediatric patients are hospital-acquired pneumonia, urinary tract infections, blood stream infections, and surgical site infections. Pediatric neutropenic patients are prone to developing bacterial infections. Treatment is often a challenge and requires initiation of empirical therapy with a broad-spectrum antibiotic. Bacterial meningitis is another cause of many pediatric intensive care unit admissions. Cefepime is a fourth-generation cephalosporin with excellent in vitro and in vivo activity against pathogens that are commonly implicated in serious pediatric infections. Cefepime has been shown to be as safe and effective as ceftazidime, cefotaxime, and cefuroxime in the treatment of lower respiratory tract infections. There was a clinical response rate in 88% to 100% of patients. In patients with urinary tract infections, primarily caused by E coli and Proteus species, cefepime 50 mg/kg/dose every 8–12 hours has been as effective and safe as ceftazidime exhibiting clinical cure and bacteriologic eradication rates above 90%. In pediatric patients with febrile neutropenin, cefepime has shown comparable efficacy rates to ceftazidime. Patients treated with cefepime developed fewer new infections and required less concomitant systemic antimicrobial therapy than ceftazidime. In several trials conducted in Europe and Latin America, patients with bacterial meningitis had similar cure rates compared to those who were treated with cefotaxime and ceftriaxone. Eradication rates of the most commonly isolated pathogens, H influenzae, N meningitidis, and S pneumoniae, were above 90%. Cefepime has a favorable safety and pharmacokinetic profile allowing for twice-daily or thrice-daily administration depending on the severity of infection. It has adequate tissue penetration and excellent activity against gram-positive and gram-negative pathogens often implicated in serious pediatric infections. Cefepime is an ideal choice for the empiric treatment of pediatric patients.

IND15 – Berna Products: Virosome vaccines: advantages in safety...

Tul15-1 The virosome vaccine principle

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Induction of an effective immune response by vaccination requires a proper processing and presentation of the vaccine antigen by antigen-presenting cells (APCs). Virosomes, derived from, e.g., influenza virus, represent a promising carrier system for delivery of antigens to APCs. Virosomes are reconstituted viral envelopes which can be generated from native virus through a detergent solubilization and removal procedure. Antigenic peptides or proteins may be encapsulated in the virosomal lumen by including them in the reconstitution mixture prior to the detergent removal step. Antigens may also be coupled to the surface of the virosomes.

Functionally reconstituted virosomes retain the cell entry and membrane fusion characteristics of the native virus. Thus, influenza-derived virosomes enter cells, including APCs, through receptor-mediated endocytosis and subsequent fusion from within acidic endosomes. In this manner, virosome-encapsulated antigens are released into the cell cytosol and, thus, into the MHC class I antigen processing pathway. On the other hand, antigens associated with the virosomal surface are introduced into the endosomal membrane, facilitating their processing in the MHC class II presentation pathway.

We have studied the capacity of influenza virosomes to prime class I MHC-restricted cytotoxic T lymphocyte (CTL) activity in mice against a peptide or whole-protein antigen. An efficient CTL response was induced with virosomes containing a synthetic peptide corresponding to a CTL epitope of the influenza nucleoprotein or containing the protein ovalbumin. The superior antigen-delivery capacity of virosomes is primarily due to their membrane fusion activity, since fusion-inactivated antigen-containing virosomes lack the ability to efficiently prime CTL activity.

Tul15-2 Influenza virosomes to fight influenza?

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Influenza vaccine will remain the cornerstone in the clinical management of influenza alongside new developments in anti NA inhibitors. The current influenza vaccines prevent hospitalization and mortality in the elderly and 'at risk' vaccine groups. However, a low proportion of elderly are non or poor responders to vaccine. Therefore, new adjuvants are urgently required.

The in vivo ferret model data will be presented which establishes that influenza virosome formulations have high efficacy in preventing influenza virus excretion and clinical symptoms. Moreover intranasal administration of virosome vaccine induces circulatory IgG antibody to influenza. Recent clinical studies of virosomes in volunteers will also be presented in the above context.

Tul15-3 Clinical experience with an inactivated virosome formulated hepatitis A vaccine

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Ten years of clinical experience with the aluminium-free, virosome formulated, inactivated hepatitis A vaccine (500 RIA units) are summarised. Data are presented on the dosing regimen (months 0, 12), on safety and immunogenicity (also in comparison to an aluminium-adsorbed vaccine), on potential interactions with other vaccines, on use in children and in